



The Effect of Multi mineral-Vitamin D Supplementation on Pregnancy Outcomes in Pregnant Women at Risk for Pre-eclampsia

Zatollah Asemi, Ahmad Esmailzadeh^{1,2}

Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Isfahan, I. R. Iran, ¹Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, ²Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence to:

Dr. Ahmad Esmailzadeh, Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, P.O. Box: 81745-151, Isfahan, Iran. E-mail: esmailzadeh@hlth.mui.ac.ir

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ABSTRACT

Background: The objective of this study was to determine the favorable effects of multi mineral-Vitamin D supplementation on pregnancy outcomes among women at risk for pre-eclampsia.

Methods: This randomized double-blind controlled clinical trial was conducted among 46 women at risk for pre-eclampsia at 27 weeks' gestation with positive roll-over test. Pregnant women were randomly assigned to receive either the multi mineral-Vitamin D supplements ($n = 23$) or the placebo ($n = 23$) for 9-week. Multi mineral-Vitamin D supplements were containing 800 mg calcium, 200 mg magnesium, 8 mg zinc, and 400 IU Vitamin D3. Fasting blood samples were taken at baseline and after 9-week intervention to measure related factors. Newborn's outcomes were determined.

Results: Although no significant difference was seen in newborn's weight and head circumference between the two groups, mean newborns' length (51.3 ± 1.7 vs. 50.3 ± 1.2 cm, $P = 0.03$) was significantly higher in multi mineral-Vitamin D group than that in the placebo group. Compared to the placebo, consumption of multi mineral-Vitamin D supplements resulted in increased levels of serum calcium ($+0.19$ vs. -0.08 mg/dL, $P = 0.03$), magnesium ($+0.15$ vs. -0.08 mg/dL, $P = 0.03$), zinc ($+8.25$ vs. -21.38 mg/dL, $P = 0.001$) and Vitamin D ($+3.79$ vs. -1.37 ng/ml, $P = 0.01$). In addition, taking multi mineral-Vitamin D supplements favorably influenced systolic blood pressure (SBP) (-1.08 vs. 6.08 mmHg, $P = 0.001$) and diastolic blood pressure (DBP) (-0.44 vs. 3.05 mmHg, $P = 0.02$).

Conclusions: Multi mineral-Vitamin D supplementation for 9-week in pregnant women at risk for pre-eclampsia resulted in increased newborn's length, increased circulating levels of maternal serum calcium, magnesium, zinc and Vitamin D, and led to decreased maternal SBP and DBP.

Keywords: Multi mineral-Vitamin D supplementation, pre-eclampsia, pregnancy outcomes

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INTRODUCTION

Due to the changes in the women's physiology and the requirements of the growing fetus, pregnancy is associated with additional requirements to several micronutrient including zinc, iron and Vitamin D.^[1,2] It is estimated that 57% of pregnant women in the

world suffer from calcium deficiency^[3] and 31–47.3% from zinc deficiency.^[4] Furthermore, the prevalence of Vitamin D deficiency during pregnancy ranges from 18% to 84% in different countries.^[5] The prevalence among Kashani pregnant women in Iran women is almost 95.8%.^[6] Micronutrient deficiencies during pregnancy might lead to spontaneous abortion, fetal malformation, growth retardation,^[7] placental abruption,^[8] increased maternal morbidity,^[9] low birth weight (LBW) babies,^[10] neonatal hypocalcaemia, and also increased incidence of autoimmune diseases.^[5]

To reduce maternal and fetal complications in pregnant women at risk for pre-eclampsia, various strategies have been suggested including, but not limited to, diet therapy and physical activity,^[11] maternal micronutrient supplementation,^[12] increased intake of marine foods^[13] and oxidative stress-lowering factors including trace elements (zinc, copper, selenium, and magnesium).^[14] Recently, few clinical trials have shown that multi mineral and/or Vitamin D supplementation might improve pregnancy outcomes.^[15,16] However, these studies were limited and the findings conflicting.

Calcium and magnesium intake might improve pregnancy outcomes through their effects on reduction of parathyroid calcium release and regulating intracellular calcium concentrations^[17] as well as increasing the sensitivity of vascular smooth muscle to nitric oxide (NO).^[18] Furthermore, zinc and Vitamin D supplementation might also influence pregnancy outcomes through the influences on regulation of insulin-like growth factor I and its receptor,^[19] regulation of gene expression associated with normal implantation and angiogenesis,^[20] improvement of insulin sensitivity.^[21] Although several studies have examined the effect of single Vitamin or mineral supplementation on pregnancy outcomes, limited data have assessed the combined effect of multi minerals and Vitamin D on these outcomes. Therefore, the current study was conducted to investigate the effects of multi mineral-Vitamin D supplementation on pregnancy outcomes in pregnant women at risk for pre-eclampsia.

METHODS

Participants

This randomized double-blind placebo-controlled clinical trial was performed in Kashan, Iran, during November 2013 to May 2014. For estimating sample size, we used a randomized clinical study sample size formula where type one (α) and type two errors (β) were 0.05 and 0.20 (power = 80%), respectively. Based on a previous study^[22] and considering newborns' weight at birth as a key variable, we considered 0.4 as standard

deviation and 0.3 kg as the difference in the mean (d). According to this, we needed 22 subjects in each group to have 80% study power. Pregnant women at risk for pre-eclampsia with positive roll-over test, primigravida, aged 18–40 years old who were carrying singleton pregnancy at their third trimester were recruited in this study. Gestational age was assessed from the date of last menstrual period and concurrent clinical assessment.^[23] Individuals with the above-mentioned inclusion criteria were called for participation in the study from among those that attended maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Iran. A total of 70 women that attended maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Iran, were screened for risk of pre-eclampsia, of whom 52 met the inclusion criteria. We did not include those with maternal severe pre-eclampsia, intra-uterine fetal death, premature preterm rupture of membrane (PPROM), completed bed rest (CBR), placenta abruption, preterm delivery, and gestational diabetes mellitus (GDM). A total of 52 pregnant women were recruited in the study and were randomly assigned to receive either the placebo ($n = 26$) or multi mineral-Vitamin D supplements ($n = 26$) for 9-week. The study was performed according to the guidelines laid down in the Declaration of Helsinki. The Ethical Committee of Kashan University of Medical Sciences approved the study and informed written consent was obtained from all participants.

Study design

Participants considered as high risk for pre-eclampsia when they had positive roll-over test.^[24] At study baseline (25 weeks of gestation), subjects were randomly assigned to receive either the placebo or multi mineral-Vitamin D supplements for 9-week. Random assignment was done by the use of computer-generated random numbers. A trained midwife at maternity clinic enrolled participants. Participants were asked not to alter their routine physical activity or usual diets and not to consume any supplements other than the one provided to them by the investigators. The placebo was provided by Share Darou Pharma Co., Tehran, Iran. The multi mineral-Vitamin D supplements (Calcicare) were containing 800 mg calcium, 200 mg magnesium, 8 mg zinc and 400 IU Vitamin D3 and provided by Vitane Pharma Co., Wolfartshausen, Germany. All subjects were also consuming 400 μ g/d folic acid from the beginning of pregnancy and 50 mg ferrous sulfate from the second trimester. We kept all supplements in a cool temperature before using. Compliance with the consumption of supplements was monitored once a week through phone interviews. The compliance, as well as dietary intakes of study participants, were also double-checked by the use of 3-day dietary records completed throughout the study.

To obtain nutrient intakes of participants based on these 3-day food diaries, we used Nutritionist IV software (First Databank, San Bruno, CA, USA) modified for Iranian foods.

Assessment of variables

Anthropometric measurements of pregnant women were assessed at baseline (25 weeks of gestation) and after 9-week of intervention (34 weeks of gestation). Body weight was measured in an overnight fasting state, without shoes and in a minimal clothing state using a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a nonstretched tape measure (Seca, Hamburg, Germany) to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared. Newborn's length and weight were measured using standard methods (Seca 155 Scale, Hamburg, Germany) during the first 24 h after birth and were recorded to the nearest 1 mm and 10 g, respectively. Newborn's head circumference was measured to the nearest 1 mm with a Seca girth measuring tape. Fasting blood samples (10 ml) from pregnant women were taken at baseline and after 9-week intervention at Kashan reference laboratory in an early morning after an overnight fast. Serum samples were analyzed for serum calcium, magnesium, zinc, iron and 25-hydroxy Vitamin D levels. Serum calcium, magnesium and iron concentrations were assayed using commercial kits (Pars Azmun Inc., Tehran, Iran). Serum zinc concentrations were examined using the appropriate kit (Elitech, France). Serum 25-hydroxy Vitamin D levels were quantified by ELISA using available kits (IDS, Boldon, UK). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was determined via a sphygmomanometer (ALPK2, Zhejiang, China). Blood pressure values were reported in millimeters of mercury.

Statistical analysis

To ensure the normal distribution of variables, Histogram and Kolmogorov-Smirnov test was applied. We used paired-samples *t*-test to identify within-group differences. Independent samples Student's *t*-test was used to detect differences between groups. Pearson Chi-square test was used to detect an association between categorical variables. $P < 0.05$ was considered as statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Among individuals in the placebo group, three women (PPROM [$n = 1$], GDM [$n = 1$] and severe pre-eclampsia [$n = 1$]) were excluded. The exclusions in the multi mineral-Vitamin D group was three persons (CBR [$n = 1$], severe pre-eclampsia [$n = 1$] and

placenta abruption [$n = 1$]). Finally, 46 participants (placebo [$n = 23$] and multi mineral-Vitamin D supplements [$n = 23$]) completed the trial [Figure 1].

The mean age of study participants was not statistically different between multi mineral-Vitamin D and placebo groups. Baseline prepregnancy weight and BMI, as well as their means before and after intervention, were not significantly different between the two groups [Table 1].

Although no significant difference was seen in newborn's weight and head circumference between the two groups, mean newborns' length (51.3 ± 1.7 vs. 50.3 ± 1.2 cm, $P = 0.03$) was significantly higher in multi mineral-Vitamin D group than that in the placebo group [Table 2]. The supplementation did not significantly influence mode of delivery.

As compared to the placebo, consumption of multi mineral-Vitamin D supplements resulted in increased levels of serum calcium ($+0.19$ vs. -0.08 mg/dL, $P = 0.03$), magnesium ($+0.15$ vs. -0.08 mg/dL, $P = 0.03$), zinc ($+8.25$ vs. -21.38 mg/dL, $P = 0.001$) and Vitamin D ($+3.79$ vs. -1.37 ng/ml, $P = 0.01$) [Table 3]. Additionally, taking multi mineral-Vitamin D supplements favorably influenced SBP (-1.08 vs. 6.08 mmHg, $P = 0.001$) and DBP (-0.44 vs. 3.05 mmHg, $P = 0.02$).

Table 1: General characteristics of the study participants^a

| | Multi mineral-vitamin D group ($n=23$) | Placebo group ($n=23$) | P^b |
|---|--|--------------------------|-------|
| Maternal age (year) | 25.0 ± 4.2 | 24.4 ± 3.6 | 0.57 |
| Height (cm) | 161.8 ± 4.5 | 161.0 ± 7.7 | 0.71 |
| Prepregnancy weight (kg) | 66.6 ± 10.9 | 66.3 ± 10.7 | 0.92 |
| Weight at study baseline (kg) | 71.0 ± 11.5 | 71.5 ± 11.6 | 0.89 |
| Weight at end-of-trial (kg) | 74.4 ± 11.3 | 75.3 ± 11.8 | 0.82 |
| Prepregnancy BMI (kg/m^2) | 25.4 ± 3.7 | 25.5 ± 3.7 | 0.91 |
| BMI at study baseline (kg/m^2) | 27.0 ± 3.8 | 27.5 ± 4.2 | 0.69 |
| BMI at end-of-trial (kg/m^2) | 28.4 ± 3.7 | 28.9 ± 4.0 | 0.63 |

^aData are means \pm SD, ^bObtained from independent *t*-test. SD=Standard deviation, BMI=Body mass index

Table 2: The effect of multi mineral-Vitamin D supplementation on pregnancy outcomes^a

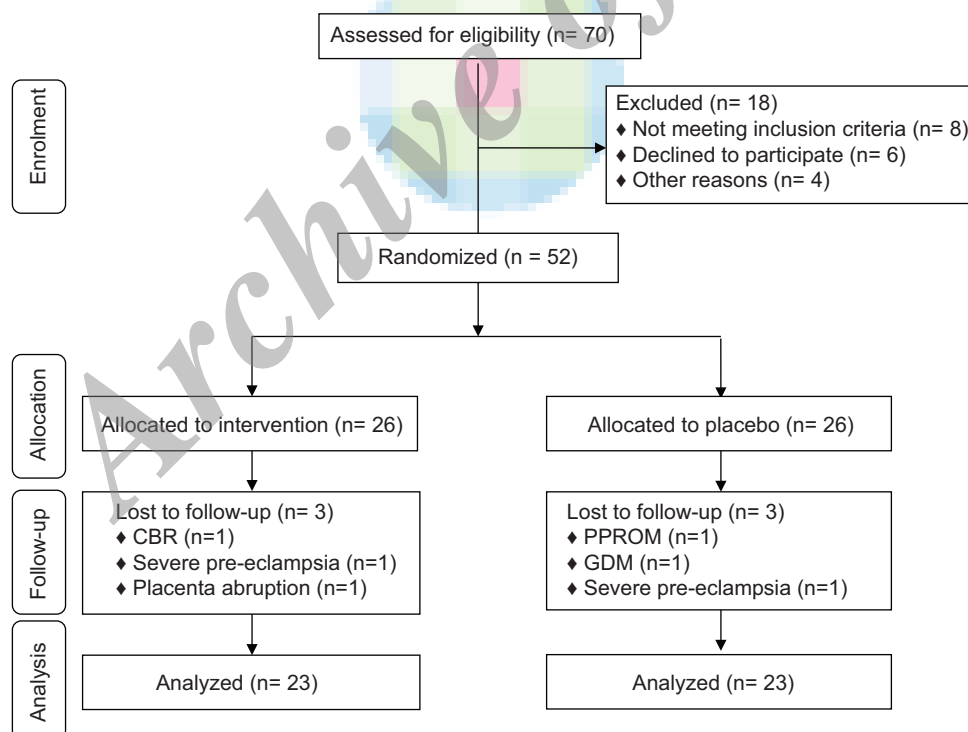
| | Multi mineral-vitamin D group ($n=23$) | Placebo group ($n=23$) | P^b |
|-----------------------------------|--|--------------------------|-------------------|
| Cesarean section (%) | 11 (47.8) | 13 (56.5) | 0.55 ^c |
| Gestational age (weeks) | 39.5 ± 1 | 39.1 ± 1.2 | 0.21 |
| Newborn's weight (kg) | 3315.7 ± 460.4 | 3300.0 ± 411.5 | 0.90 |
| Newborn's length (cm) | 51.3 ± 1.7 | 50.3 ± 1.2 | 0.03 |
| Newborn's head circumference (cm) | 35.5 ± 1.2 | 35.2 ± 1.5 | 0.41 |
| Severe preeclampsia rate (%) | 1 (3.8) | 1 (3.8) | 1.00 ^c |
| GDM rate (%) | 0 (0) | 1 (3.8) | 0.31 ^c |

^aValues are means \pm SD, ^bObtained from independent *t*-test, ^cObtained from Pearson Chi-square test. GDM=Gestational diabetes, SD=Standard deviation

Table 3: Means (\pm SD) of serum minerals, vitamin D levels, BP and dietary intakes at baseline and after the intervention

| | Multi mineral-vitamin D group (n=23) | | | | Placebo group (n=23) | | | | <i>P</i> ^b |
|---|--------------------------------------|--------------|--------------|-----------------------|----------------------|--------------|--------------|-----------------------|-----------------------|
| | Week 0 | Week 9 | Change | <i>P</i> ^a | Week 0 | Week 9 | Change | <i>P</i> ^a | |
| Serum minerals, Vitamin D levels and BP | | | | | | | | | |
| Calcium (mg/dL) | 8.66±0.49 | 8.85±0.63 | 0.19±0.39 | 0.03 | 9.16±0.35 | 9.08±0.37 | −0.08±0.42 | 0.35 | 0.03 |
| Magnesium (mg/dL) | 1.80±0.21 | 1.95±0.22 | 0.15±0.28 | 0.01 | 2.12±0.32 | 2.04±0.30 | −0.08±0.42 | 0.37 | 0.03 |
| Zinc (mg/dL) | 57.08±8.13 | 65.33±12.55 | 8.25±11.79 | 0.003 | 88.09±36.7 | 66.71±13.14 | −21.38±36.47 | 0.01 | 0.001 |
| Iron (mg/dL) | 94.04±56.88 | 75.52±25.62 | −18.52±50.73 | 0.09 | 97.47±84.44 | 103.34±68.26 | 5.87±69.54 | 0.69 | 0.18 |
| Vitamin D (ng/mL) | 18.25±6.74 | 22.04±9.26 | 3.79±8.17 | 0.04 | 15.58±6.53 | 14.21±6.21 | −1.37±2.23 | 0.02 | 0.01 |
| SBP ^c (mmHg) | 113.47±4.86 | 112.39±6.88 | −1.08±5.42 | 0.34 | 110.00±6.03 | 116.08±5.83 | 6.08±7.82 | 0.001 | 0.001 |
| DBP ^d (mmHg) | 66.30±6.43 | 65.86±7.17 | −0.44±5.41 | 0.70 | 66.95±5.38 | 70.00±5.83 | 3.05±4.94 | 0.007 | 0.02 |
| Dietary intakes | | | | | | | | | |
| Energy (kcal/d) | 2388±179 | 2352±161 | - | 0.47 | 2343±314 | 2373±205 | - | 0.70 | - |
| Carbohydrate (g/d) | 334±34 | 320±35 | - | 0.84 | 324±61 | 327±48 | - | 0.90 | - |
| Fat (g/d) | 86±13 | 83±12 | - | 0.21 | 91±16 | 83±18 | - | 0.84 | - |
| Protein (g/d) | 89±16 | 88±11 | - | 0.62 | 87±20 | 87±20 | - | 0.73 | - |
| Dietary fiber (g/d) | 19.9±4 | 17.9±3.6 | - | 0.08 | 19.3±4.7 | 17.8±5.2 | - | 0.26 | - |
| Calcium (mg/d) | 1131.7±224.1 | 1156.2±176.6 | - | 0.69 | 1132.1±175.7 | 1106.5±164.7 | - | 0.63 | - |
| Phosphorus (mg/d) | 1193.3±203.6 | 1197.9±135.1 | - | 0.93 | 1153.1±198.7 | 1210.5±271.8 | - | 0.48 | - |
| Magnesium (mg/d) | 292.5±73.1 | 274.9±49.3 | - | 0.33 | 270.8±57.2 | 277.7±81.0 | - | 0.78 | - |
| Zinc (mg/d) | 10.9±2.5 | 9.9±2.6 | - | 0.22 | 10.7±3 | 9.9±3.7 | - | 0.45 | - |

^aIndicates within-group differences (paired samples *t*-test), ^bIndicates between group differences (independent samples *t*-test), ^cSBP=Systolic blood pressure, ^dDBP=Diastolic blood pressure, BP=Blood pressure, SD=Standard deviation

**Figure 1: Summary of patient flow**

We did not find a significant difference in mean changes of maternal serum iron levels comparing the two groups. Within-group comparisons in the multi mineral-Vitamin D group revealed a significant increase in serum calcium (+0.19 mg/dL, *P* = 0.03), magnesium

(+0.15 mg/dL, *P* = 0.01), zinc (+8.25 mg/dL, *P* = 0.003) and Vitamin D levels (+3.79 ng/ml, *P* = 0.04). In addition, within-group comparisons in placebo group revealed a significant reduction in serum zinc (-21.38 mg/dL, *P* = 0.01), Vitamin D levels (-1.37 ng/ml, *P* = 0.02), and

a significant increase in SBP and DBP (+6.08 mmHg; $P = 0.001$, +3.05 mmHg; $P = 0.007$, respectively). We found no statistically significant difference between the two groups in terms of dietary intakes of energy, carbohydrate, fat, protein, dietary fiber, calcium, phosphorus, magnesium, and zinc throughout the study.

DISCUSSION

This study showed that consumption of multi mineral-Vitamin D supplements for 9-week among pregnant women at risk for pre-eclampsia resulted in a significant increase in newborn's length, maternal serum calcium, magnesium, zinc and Vitamin D levels, and also a significant reduction in maternal SBP and DBP. We failed to find any significant effect of multi mineral-Vitamin D supplementation on gestational age, mode of delivery, newborns' weight, and head circumference as compared to the placebo.

Pregnant women are susceptible to micronutrients deficiency especially calcium, zinc and Vitamin D due to the growing fetus and the development of the fetal skeleton in the third trimester. Micronutrients deficiency during pregnancy would result in several complications in maternal and fetal life.^[9,10] Our data showed that the use of multi mineral-Vitamin D supplements for 9-week among pregnant women at risk for pre-eclampsia led to increased newborns' length, but did not affect newborns' weight and head circumference. This finding was in line with the reports of Sabour *et al.*^[25] where higher newborns' length was seen in mothers who had adequate calcium and Vitamin D intake than those with the inadequate intake. However, oral magnesium supplementation (365 mg/d) among normotensive primigravid mothers who were between 13 and 24 weeks of gestation did not result in a significant difference in SBP, DBP, incidence of pre-eclampsia, fetal growth retardation, preterm labor, birth weight and gestational age at delivery compared with placebo.^[26] Maternal supplementation with folic acid + iron + zinc has led to an increase in mean height among children aged 6–8 years.^[27] Mild to moderate maternal zinc deficiency has also resulted in LBW, intra-uterine growth retardation, and preterm delivery, whereas severe zinc deficiency led to abortion and congenital malformations.^[28] Furthermore, Kalra *et al.*^[29] has reported that the intake of either one oral dose of 1500 µg Vitamin D₃ or two doses of 3000 µg Vitamin D₃ in the second and third trimesters has been resulted in increased birth weight, length, and head circumference. The particular mechanisms through which prenatal multi mineral-Vitamin D supplementation may have influenced postnatal growth patterns are unknown. Zinc plays an important role in the regulation of insulin-like growth factor I and its receptor,^[19] thereby may be act as an activator of insulin-like growth factor I

activity within osteoblasts and promoting bone growth.^[30] Furthermore, Vitamin D might be associated with a taller knee-heel length, suggesting influences on long bone growth.^[31]

The current study revealed that consumption of multi mineral-Vitamin D supplements for 9-week among pregnant women at risk for pre-eclampsia resulted in a significant increase in maternal serum calcium, magnesium, zinc and Vitamin D levels. Inconsistent with our study, Firouzabadi *et al.*^[32] observed increased levels of serum calcium and Vitamin D with 1000 mg/day plus Vitamin D 100,000 IU/month supplementation for 6 months in infertile women with polycystic ovary syndrome. Supplementation with 30 mg elemental zinc during the last 2 trimesters of pregnancy has also been linked to higher serum zinc concentrations in the zinc-supplemented group than in the placebo group.^[33] Similar increases in serum Vitamin D and calcium levels were also documented with use of Vitamin D^[34] and calcium^[16] supplements during pregnancy.

We demonstrated that multi mineral-Vitamin D supplementation for 9-week among pregnant women at risk for pre-eclampsia led to a significant reduction of maternal SBP and DBP. Pfeifer *et al.*^[35] has shown that receiving 1200 mg calcium plus 800 IU Vitamin D₃ compared with 1200 mg calcium/day for 8 weeks in elderly women resulted in increased serum Vitamin D and decreased SBP, but did not influence DBP. Oral magnesium supplementation (600 mg of pidolate magnesium daily) for a 12-week period has also been resulted in significant reductions in mean 24-h systolic and in patients with mild hypertension.^[36] In addition, the use of 200 mg magnesium, 30 mg zinc, 200 mg Vitamin C and 150 mg Vitamin E significantly reduced SBP, DBP and mean blood pressure in type 2 diabetic patients after 3 months.^[37] The same findings have also been reported with Vitamin D supplementation in hypertensive patients after 3 months.^[38] Several mechanisms can explain the beneficial effects of multi mineral-Vitamin D supplementation on blood pressure. Firstly, calcium may act as a regulatory factor of the renin-angiotensin system and thus might result in blood pressure regulation via altering cellular concentrations of sodium and calcium ions.^[38] Secondly, magnesium might have antihypertensive effects due to increased sensitivity of vascular smooth muscle to NO or decreased production of vasoconstrictor prostanoids.^[18] Furthermore, Vitamin D has a critical role in the regulation of the renin-angiotensin system.^[38,39]

Several limitations must be considered in the interpretation of our findings. Small sample size was a main limitation of our study. Further trials with a large sample size would be needed to confirm our findings. Moreover, due to budget limitations, we were unable to

assess the effect of supplementation in the later life of born babies. In the current study, we could not examine the effects of multi mineral-Vitamin D supplementation on the biochemical indicators of newborn infants. Furthermore, other indicators of pregnancy outcome, including hospitalization in Intensive Care Unit could not be assessed.

In conclusion, multi mineral-Vitamin D supplementation for 9-week in pregnant women at risk for pre-eclampsia resulted in increased newborn's length, increased circulating levels of maternal serum calcium, magnesium, zinc and Vitamin D, and led to decreased maternal SBP and DBP, but did not influence gestational age at delivery, mode of delivery, newborns' weight and head circumference.

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